

Effects of Insight Meditation on the Morphology of the Hippocampal Formation

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To my father.

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CONTENTS

ACKNOWLEDGEMENTS	3
LIST OF TABLES	6
LIST OF FIGURES	7
ABSTRACT	8
EFFECTS OF INSIGHT MEDITATION ON THE MORPHOLOGY OF THE	
HIPPOCAMPAL FORMATION	9
Introduction	9
Stress	9
Meditation	11
Neuroplasticity and the Hippocampus	14
Further Implications and Study Hypothesis	16
Methods	19
Subjects and Sociodemographic Assessment	19
Meditation Technique and Biometric Measurement	19
MRI Image Acquisition	20
MRI Image Analysis	20
Assessment of Hippocampal Volume	21
Reliability Assessment	23
Voxel-Based Morphometry	24
Statistical Analysis	25
Results	27
Manual Segmentation	27
Voxel-Based Morphometry	30
Discussion	43
Meditation and Gender Differences in Hippocampal Volume	43
Meditation and Its Effects on a Whole Brain Scale	52

General Methodological Remarks	58
CONCLUSION	60
REFERENCES	62

LIST OF TABLES

1	Descriptive statistics of meditators and controls	19
2	Descriptive statistics of hippocampal volume of the whole sample	27
3	Relationship between gray matter density and group membership	34
4	Relationship between gray matter density and change in breathing rate \dots	36
5	Gray matter density and group membership in men	39
6	Grav matter density and group membership in women	41

LIST OF FIGURES

1	View on MNI DISPLAY	28
2	Relationship between left and right hippocampal volume	28
3	Hippocampal volume in female meditators and controls	29
4	Hippocampal volume in male meditators and controls	30
5	Hippocampal volume in male meditators	31
6	Hippocampal volume in male controls	32
7	Comparison of hippocampal volume in male meditators and controls. $\ldots\ldots$	34
8	Gray matter density in the left fusiform gyrus	35
9	Gray matter density in the left superior frontal gyrus	37
10	Gray matter density in the right posterior cingulate	38
11	Gray matter density in the right inferior temporal gyrus	40
12	Gray matter density in the left thalamus	42
13	Overview over the proposed underlying mechanism	45
14	Example of a cluster distribution in an ROI-analysis.	53

ABSTRACT

Objective: Only recently it was found that certain meditative techniques might be capable to induce changes in the brain on a morphological level. As it has been known for quite a while that meditation is able to alter the human response to stress and because at this point there were well grounded ideas about the mechanisms underlying the human stress response, it was suggestive to combine the knowledge within the field of stress research and in the area of meditation research to try to get an idea of the mechanisms that might bring about the effects that are believed to accompany meditative practice. As especially the hippocampus is said to play an important role within the human stress response system, the current study tested, whether meditation has an influence on the morphology of this particular brain region. Methods: Hippocampal volume of 20 meditators, who practiced Yoga Insight Meditation, and 15 non-meditators was manually segmented and compared. Additionally a VBM-analysis was conducted to analyze the sample on a whole-brain level as well and to try to cross validate the results from the manual segmentation. Results: Manual segmentation revealed that meditators show a clear trend to higher hippocampal volume in comparison to non-meditating controls, although the result could not reach significance. Analyzing women and men separately it could be found that the effect in the whole sample was mainly driven by male meditators: Female hippocampal volume was nearly unchanged between practitioners and non-practioners, while in men there was a difference in hippocampal volume between meditators and male control subjects that reached the same significance level as the difference in the whole sample. The supplemental VBM-analyses detected higher gray matter concentration in the left fusiform gyrus when comparing meditators and controls in the whole sample. Checking for the influence of meditative experience it was found that the left superior frontal gyrus and the posterior cingulate cortex bilaterally had increased gray matter density. Finally, analyzing only men unveiled a region in the right inferior temporal gyrus with higher gray matter density in meditating men than in non-practicing controls. Thus, the results of the manual segmentation could not be cross validated. Conducting the same analysis for the female sample showed higher gray matter density in the left thalamus in meditating women. Discussion / Conclusion: These results suggest that meditative practice is capable to induce morphological changes in the brain. Furthermore meditation seems to involve, or to affect respectively, a specific set of brain regions and this set might be different for men and women. In addition the relation of meditation to another complex cognitive task, namely attention, and to the human stress response system is discussed and a model of a possible underlying mechanism is presented. General methodological considerations and an outlook into future research complete the study.

EFFECTS OF INSIGHT MEDITATION ON THE MORPHOLOGY OF THE HIPPOCAMPAL FORMATION

Introduction

Stress

A study in which young healthy adults were confronted with a stress task in a functional magnetic resonance imaging (fMRI) setting revealed that the human stress response is negatively correlated with the activity of the hippocampus in a special group of male participants, the so called responder [Pruessner et al., 2007]. This pointed to the fact that the hippocampus suppresses activity in one of the main parts of the human stress system, namely the hypothalamic-pituitary-adrenal (HPA)-axis.

Self-esteem and locus of control as measured by according questionnaires were positively correlated with hippocampal volume as accessed by manual segmentation from high-resolution magnetic resonance imaging (MRI) data in young as well as in elderly healthy adults [Pruessner et al., 2005]. The same study disclosed a negative correlation between the cortisol response to stress accessed by saliva samples and the hippocampal volume in young adults [Pruessner et al., 2005]. Thus, it could be assumed that variability in hippocampal volume determines how strong its influence on the HPA-axis is.

Although it is difficult to give a concise definition of the term stress including all present types and the day-to-day understanding of stress, the following attempt provides a workable and operational definition that is suitable for the purposes of this study. So, in the present context stress is considered to be a specific state of an organism that is defined by the behavioral and physiological responses of this organism to a certain situation, event or experience. The conditions under which stress appears can be called stressor [Weiner, 1992]. A stressor can have an impact on the organism for several minutes or may last for a long period of time. The first case can be called an acute stressor, whereas the second case should be referred to as chronic stress [Ockenfels et al., 1995]. An example for an acute stressor may be a public speaking task, and unemployment could be an example for a chronic stressor. Furthermore stressors can be distinguished in terms of their correspondence to a real object:

Reactive stressors are existing and real in opposite to anticipatory stressors that are

not actually present. An additional differentiation makes the point to be made here more distinct and fine: the categorization into physical and psychological stressors. In spite of representing a threat to the physical integrity of the organism, a psychological stressor aims at the social status of the organism [Herman et al., 2003]. The status of emotional stressors is not clearly defined. But despite of some reasons for considering them as a class of their own, it is equally plausible to let them be among psychological stressors. Tasks containing both uncontrollable and social-evaluative elements are said to be associated with the largest cortisol and adrenocorticotropin hormone changes and the longest times to recovery, i.e. induce the highest levels of stress. In particular that means that cortisol is not responsive to all types of stressors in the same way Dickerson & Kemeny, 2004. The possible underlying mechanism of the human stress response can be described as follows: If an organism is confronted with a certain stressor, the corresponding neuronal activation pattern will on the one hand initiate a cascade of molecular actions leading amongst other things to the secretion of hormones, which create a specific psychological response. On the other hand in mutual interaction the activation pattern will create a certain behavioral "fight-or-flight" response. The molecular cascade forms the HPA-axis and starts with the arrival of the neuronal activation pattern at the level of the paraventricular nucleus of the hypothalamus. The activation of this nucleus will lead to the expression of corticotropin releasing hormone (CRH). CRH in return will activate the anterior pituitary gland, which will secrete adrenocorticotropin hormone (ACTH) into the blood stream. ACTH will activate the adrenal cortex. The activated adrenal cortex stimulates the adrenal gland. This stimulation will in the last step lead to the production and releasing of cortisol into the blood stream [Sawchenko et al., 2000]. This underlying mechanism makes it possible to measure the stress response [Sapolsky et al., 2000, Sapolsky, 2000]. It is now well known that the HPA-axis and several structures of the limbic system are strongly interconnected and especially the hippocampal formation [Bratt et al., 2001] may serve as a regulatory unit of the HPA-axis and therefore of the stress response via inhibitory efferents to the hypothalamus [Chozick, 1983, Herman et al., 2003]. Thus, there is a well-established corpus of knowledge about the rich interactions between major components of the limbic system (hippocampus, hypothalamus, and amygdala), modulating

neurotransmitters and their relations with the HPA-axis as well as with the sympathicoadrenomedullary system, the second major system that mediates the stress response in humans [Fuchs & Flugge, 2003]. Using a psychosocial stress task different studies revealed that the stress response is positively correlated with cortisol levels [Kirschbaum et al., 1995b, Kirschbaum et al., 1995a, Sapolsky et al., 2000, Sawchenko et al., 2000]. In short: If those facts are added together, one can consequentially conclude that a stressor triggers the deactivation of the hippocampus and thereby subsequently a cortisol response.

When 21 healthy adults underwent structural magnetic resonance imaging and completed a stress profile questionnaire, researchers found that greater psychological stress correlated significantly and more strongly with anterior than posterior hippocampal volume. The authors thought that their findings suggest that psychological stress may be associated with structural alterations in the anterior hippocampal formation and that this relationship may differ along the rostrocaudal axis of the hippocampus [Szeszko et al., 2006]. But in accordance to what was mentioned above, an alternative reading would be to assume that levels of perceived stress develop depending on the size of the hippocampus and the according strength of the cortisol response.

Earlier it was found that self-esteem is negatively correlated with levels of free cortisol in Salivette sampling, when participants are exposed to a computer-generated mental stress task [Pruessner et al., 1998]. Thus the conclusion seems plausible that depending on the occurring levels of perceived stress - in the course of time - corresponding personality traits evolve.

Meditation

Meditation can be seen as a specific technique or as a certain state of consciousness. The latter understanding of meditation can be called relaxation response and can be construed as the direct outcome of the first one, the meditative technique. The relaxation response can be considered to be an overall slow-down of several physiological systems [Benson et al., 1977, Benson, 1982] and an additional more fine and distinct pattern of superimposed changes that are specific to the particular technique employed [Schwartz et al., 1978]. These effects can be further distinguished

into state and trait effects referring to effects of actually being in a meditative state and long-term effects without actively set into a specific state of awareness. Thus, meditation research for the purposes of the current study refers to research concerned with specific mental techniques and their impacts, which implicate certain underlying mechanisms. Those mental, or meditative techniques respectively are understood here as practices of self-regulation of body and mind processes, which result in a specific attentional condition [Cahn & Polich, 2006]. Because of a wide variety of techniques it is helpful to order them on a scale between the both most extreme, or pure forms respectively: mindfulness and concentration. Although probably there will not be an example of a pure case and most techniques share some essential features e.g. the development of a transcendent observer's perspective or resulting states, this distinction emphasize the fact that within the group of meditative techniques there are some crucial differences that have to be taking into consideration when dealing with meditation in a scientific setting, as these differences might elicit distinct effects [Carlson et al., 2004, Zhang et al., 1993]. In mindfulness practice feelings, sensations and thoughts are allowed and observed from an attentive, non-attached position of the mind, without any judgment or analysis. A variation of this category tries to clear the mind of all thoughts. In contrast, concentrative techniques use the focusing of attention on a specific object, sensation or mental activity to let a meditative state emerge [Cahn & Polich, 2006]. The latest developments in the field of meditation research make it seem plausible and advisable to use a definition, based on newly found results to facilitate more precise future work, i.e. meditation should be regarded as an attentional training. This enables researchers to interpret neurophysiological and imaging data as well as findings out of the realm of attention research more integrated and more easily.

A possible mechanism underlying the effects of meditation was proposed by Newberg and Iversen [Newberg & Iversen, 2003]: In general meditative techniques are assumed to activate the prefrontal (PFC) and cingulate cortex by willingly and actively intent to focus on a certain object or keep the mind in an only watching state. This activation may lead to an innervation of the reticular nucleus of the thalamus as part of the global attentional network. The thalamus processes information further via the lateral geniculate and the lateral posterior nuclei. Especially the lateral posterior

nucleus of the thalamus feeds information into the posterior superior parietal lobule (PSPL). Thus, activation of the prefrontal cortex increases activity in the reticular nucleus resulting possibly in a decreased sensory input into the PSPL. This functional deafferentation that is related to increased gaminobutyrate (GABA) release would provide the basis of filtering out more distracting outside stimuli and result in less sensory input to the PSPL as well as the visual cortex, thus enhancing the sense of focus and alter the perception of the self. The partial deactivation of the PSPL might lead to a stimulation of the hippocampus and other limbic structures, because of the inverse modulation of the hippocampal activity in relation to cortical function, i.e. the hippocampus acts to modulate cortical arousal and responsiveness via rich and extensive interconnections with the prefrontal cortex, the amygdala and the hypothalamus. Subsequent activation of the amygdala is probably able to stimulate the hypothalamus yielding in the activation of the peripheral parasympathetic system. The recruitment of the parasympathetic system then might be the reason for the subjectively and objectively reported relaxation, reflected in reduced heart and respiratory rate. Slowing down breathing and heartbeat rate would possibly result in stopping the paragigantocellular nucleus of the medulla innervating the locus ceruleus (LC). Because the LC distributes norepinephrine to the hypothalamic paraventricular nucleus this nucleus will be less active and as it is responsible for the production of CRH, there will be less secretion of CRH. CRH normally stimulates the anterior pituitary gland to release ACTH. ACTH in turn activates the adrenal cortex to produce cortisol. Hence, one this way meditation would decrease cortisol levels. Decreased blood pressure accompanying the relaxation would cause the caudal ventral medulla to decrease its GABAergic inhibition of the supraoptic nucleus of the hypothalamus (SN) what in turn would cause the SN to release vasoconstrictor arginine vasopressin (AVP). AVP again can contribute to the general maintenance of positive affect and decreased self-perceived fatigue and arousal and may also be a reason for reported enhancements in learning and memory related to meditation. Another way the increased activity of the PFC might deploy its further effects is via the production of free synaptic glutamate. Glutamate can stimulate the hypothalamic arcuate nucleus that on the other hand releases beta-endorphin (BE). BE is known to depress respiration, reduce fear and pain and produce sensations of joy and euphoria.

Several studies detected increased cerebral blood flow in the hippocampus bilaterally, parietal and occipital association regions and overall decreases in orbitofrontal, dorsolateral, prefrontal, anterior cingulate cortices, temporal and inferior parietal lobes, caudate, thalamus, pons and cerebellum related to meditative practice [Lou et al., 1999] with each activation pattern related to a specific type of meditational technique. A generally found increased activity of the hippocampal formation was related to a detected increased of theta activity [Cahn & Polich, 2006]. Subsequent functional studies confirmed the idea that meditative states are reflected in increased activity of areas subserving attention (dorsolateral prefrontal and parietal cortex) and those responsible for arousal and autonomic control (limbic regions, midbrain, pregenual anterior cingulate cortex) [Lazar et al., 2000]. Likewise it became apparent that meditation is capable to change humans response to pain: When scanning long-term meditators, who were not actually in a meditative state, in an fMRI-study while they were exposed to thermally induced pain, they showed up to 50% fewer voxels responding in the thalamus and total brain than healthy matched controls. After the controls learned the according technique and practiced it for five months, their response decreased by 40-50% in the thalamus, prefrontal cortex, total brain, and marginally in the anterior cingulate cortex [Orme-Johnson et al., 2006].

Therewith one can realize that meditation can influence human reactivity towards different environmental impacts as well as toward internal processes. Especially the last mentioned study suggests the guess that such influence should be reflected on an anatomical level as well and therefore researchers should be able to demonstrate and verify it morphologically. In another fMRI-study that focused on the role of meditative experience expert meditators had less brain activation than novices in regions related to discursive thoughts and emotions and more activation in regions related to response inhibition and attention in response to distracter sounds.

Correlation with hours of practice suggested possible plasticity in these mechanisms [Brefczynski-Lewis et al., 2007].

Neuroplasticity and the Hippocampus

In general there are good arguments to believe that there is a capacity for local plastic change in the structure of the healthy adult human brain in response to environmental demands [Maguire et al., 2000, Maguire et al., 2006b, Maguire et al., 2006a]. And yet, the idea of experience-dependent plasticity is still controversial [Davidson, 2005]. Remodeling processes are thought to be capable to account for long-lasting changes (trait effects) in the brain. The fundamental underlying synaptic plasticity could be due to the recruitment of existing but not yet used synapses or to the development of new synapses. In greater detail that would implicate that cortical plasticity due to experience might be caused by either greater arborization per neuron, increased glial volume or increased regional vasculature [Lazar et al., 2005]. The latter could maybe explain some functional results, too. But increased cortical thickness for example may also be due to a decreasing rate of neuronal degeneration induced by meditation. The study referred to at the beginning of this sub-chapter was one of the earliest imaging studies that proofed that experience could induce detectable changes on a morphological level in the brain [Maguire et al., 2000]: Maguire and his coworkers tested London taxi drivers with extensive navigation experience and compared their brains to control persons who did not drive taxis. They found a posterior hippocampus that was significantly larger in taxi drivers relative to those of control subjects. Additionally a more anterior hippocampal region was larger in control subjects than in taxi drivers. Hippocampal volume correlated with the amount of time spent as a taxi driver. Researchers concluded that there is the capacity for local plasticity in the brain as response to its day-to-day demands. So, not only could this study show that the brain has the capability to change in accordance to its milieu, but particularly it could demonstrate the plasticity of the human hippocampus. Finally, in 2005 a group of researchers at Harvard Medical School assessed cortical thickness in people with extensive Insight Meditation experience and of people without any meditative experience using magnetic resonance imaging. The results brought about a positive correlation between meditative practice and cortical thickness in several brain regions [Lazar et al., 2005]. Thus in sum it seems obvious, that meditative practice is able to shape different cortical areas.

Further support entailing also some possible explanations for the perspective that the hippocampus is an especially plastic and vulnerable region of the brain comes from stress research: As described, the hippocampus is a target of stress hormones and also responds to gonadal, thyroid, and adrenal hormones, which modulate changes in synapse formation and dendritic structure and regulate dentate gyrus volume during development and in adult life. Two forms of structural plasticity can be derived from these facts: Repeated stress causes atrophy of dendrites in the CA3 region, and both acute and chronic stress suppresses neurogenesis of dentate gyrus granule neurons. Besides glucocorticoids, excitatory amino acids and N-methyl-D-aspartate (NMDA) receptors are involved in these two forms of plasticity as well as in neuronal cell death that is caused in pyramidal neurons by seizures and by ischemia. Hence, these are the two main forms of structural plasticity relevant to the human hippocampus, which undergoes a selective atrophy in a number of disorders, accompanied by deficits in declarative, episodic, spatial, and contextual memory performance [McEwen, 1999]. In a recent voxel-based morphometry (VBM) study of mindfulness meditators and non-meditators, that were matched for sex, age, education, and handedness, meditators showed greater gray matter concentration in regions that are typically activated during meditation and those subserving functions cultivated by meditation practice: the right insula, left inferior temporal gyrus, left precentral gyrus, and the right hippocampus [Holzel et al., 2007]. Hence, it becomes clear that meditative practice might particularly be able to increase hippocampal volume.

Further Implications and Study Hypothesis

As researchers could show in several studies that meditative practice is negatively correlated with the cortisol response to stress

[Jevning et al., 1978, MacLean et al., 1994, MacLean et al., 1997], it can be inferred now that an increase in hippocampal volume might lead to a stronger dampening effect on the cortisol response to an acute stressor.

Already in the 1970ies the connection between stress research on the one hand and meditation research on the other hand could be shown in form of studies that displayed biochemical changes accompanying meditational practice. Changes in prolactin [Jevning et al., 1978], cortison [Jevning et al., 1978], proteins in the saliva [Morse et al., 1981b, Morse et al., 1981a] and phenylalanine [Jevning et al., 1977] could be found and systematically pointed to the physiologically effects of meditation. Since these early results there has been great progress in both fields. In recent years as shown above especially the development of brain imaging techniques like positron

emission tomography (PET) or MRI promoted understanding to a new level. Although there are still studies that for instance cannot find any significant effects of certain meditative techniques on specific mood symptoms, e.g. depression or anxiety, in clinical populations [Toneatto & Nguyen, 2007], it already seems quite ascertained that meditative practice has an impact on certain human personality characteristics: Comparing the effects of a mindfulness meditation and a somatic relaxation training with a control group it came out that both groups experienced significant decreases in distress as well as increases in positive mood states over time, compared with the control group. Although there were no significant differences between meditation and relaxation on distress and positive mood states over time, the meditation group showed a larger effect size for positive states of mind than relaxation. The meditation group also demonstrated significant pre-post decreases in both distractive and ruminative thoughts/behaviors compared with the control group [Jain et al., 2007]. Teaching healthy participants a simple mantra-based meditation technique, researchers tested for changes in mood states, perceived stress, neuroticism and anxiety after a short training phase using according questionnaires. All scales improved significantly after instruction, with reductions from baseline that ranged from 14% to 36%. Researchers concluded that even a short period of practicing a simple meditation technique can improve negative mood and perceived stress in healthy adults, which could yield long-term health benefits and that the frequency of practice does affect the outcome. Additionally they assumed that those most likely to experience negative emotions might benefit the most from such an intervention [Lane et al., 2007]. Further on several studies revealed that meditative practice is negatively correlated with levels of perceived stress

[Cahn & Polich, 2006, Herzog et al., 1991, Lou et al., 1999, Travis et al., 2004]. So, putting it all together and using all prior arguments, one can get an overall picture that might integrate all mentioned facts and in the end it seems feasible to assume that meditation via the outlined ways lowers cortisol levels and thereby leads to lower levels of perceived stress and over time to changes in personality traits.

This very idea of the according underlying mechanism worked out up to this point also contains the hypothesis of this study: Meditation is positively correlated with hippocampal volume. Up to now researchers could not get coherent results for the hippocampus. The main reason for this is that either the applied method was not able to examine subcortical structures in principle, as is the case for cortical thickness analyses, or the according tool for automatic segmentation was not precise enough to find sound results for subcortical structures: Automated tools are able to give a general outline of sub-cortical structures as the hippocampus and the amygdala, but normally the gray / white matter contrast resolution of the scans is not sufficient for such programs to determine the volumes of subcortical structures precisely. Further on automated, voxel-based analyses are not able to create valid results due to their computational limits, as long as they are used in isolation [Bookstein, 2001]. Because of that the only existing studies of interest in this context, namely the one of Sara Lazar [Lazar et al., 2005] and the VBM-equivalent of Britta Holzel [Holzel et al., 2007] cannot answer the question, whether or not meditative practice might have an influence on hippocampal volume and if of which kind: Therefore in this study the data of Sara Lazar's study was used for manual segmentation of hippocampal volume in combination with VBM to cross validate the results and get a clearer picture of how meditation might influence hippocampal morphology.

Methods

Subjects and Sociodemographic Assessment

Personality data was transferred after the assessment of hippocampal volumes was finished: In total 35 participants took part in the original study. 20 of them had extensive training in Insight meditation and 15 were control participants. Practitioners had on average between 9.1 ± 7.1 years of experience and practiced 6.2 ± 4.4 h per week. Furthermore practitioners had to participate in an Insight Meditation retreat that lasted at least seven days and included ten hours of daily meditation. The control participants had neither experience in meditation, nor in yoga. Both groups where matched for gender (meditators 65% male, controls 67%), age (meditators 38.2 years old, controls 36.5 years old), and level of education (meditators 17.3 years, controls 17.5 years). All participants were Caucasian except one meditator, who was Mexican-Caucasian (see *Table 1*).

Table 1: Descriptive statistics of meditators and controls.

	Gender	Age	Years of Education
Meditators	65% (male) 35% (female)	38.15 (SD = 8.586)	17.30 (SD = 2.105)
Controls	66.7% (male) 33.3% (female)	36.47 (SD = 9.054)	17.53 (SD = 1.685)

All participants were physically and psychologically healthy. All participants provided written, informed consent to the original study and the study was approved by the Institutional Review Board at the Massachusetts General Hospital.

Meditation Technique and Biometric Measurement

The specific kind of meditation exploited in this study, namely Insight Meditation, also called Vipassana meditation, is a simple technique, which depends on direct experience and observation. Its aim is to bring full awareness to the mind, body and all sensations, i.e. to be fully present, thus developing some specific attentional abilities. In particular, this practice tries to train awareness for the present moment that is free of any judgments and cognitive elaborations. The meditation object is one's own consciousness, although it can be further refined to be one's consciousness while observing. Insight meditation has been used as one of two poles for the categorization of types of Buddhist meditation, the other being samatha, which is a focusing,

pacifying and calming meditation.

Change in respiration rate is said to be the best indicator for meditational experience so far [Lazar et al., 2005]. Therefore, also in the current study this biometrical measurement was used as objective criterion to determine and assign meditational experience to the study participants. Originally this marker was assessed by calculating the average breathing flow, i.e. the actual trace of every breath, of a six minutes baseline period and subsequently comparing it to the average breathing flow of the first six minutes of a meditation period.

MRI Image Acquisition

The MRI scans were acquired at the Massachusetts General Hospital, Boston. Two 3D magnetization prepared rapid gradient echo (MPRAGE) structural scans (repetition time: 7.25 ms, time to echo: 3 ms, flip angle: 7°, in-plane resolution: 1.3 mm, slice thickness: 1 mm) were created of each participant using a Sonata 1.5-T whole-body high-speed imaging device (Siemens, Iselin, NJ; 3-axis head coil). These two scans where motion-corrected and averaged together to one resulting high-resolution image.

$MRI\ Image\ Analysis$

Merged imaging data was downloaded in COR-file format as used by FreeSurfer [CorTechs, 2007] via an anonymous file transfer protocol (FTP) from a server at Harvard Medical school onto a Macintosh Powerbook G4 (Mac OS X, version 10.4.9). Images were then locally converted into Medical Imaging NetCDF (MINC)-file format using NeuroLens [Hoge, 2007]. Subsequently all images were preprocessed using a graphical user interface for structural processing (GUISPRO) developed at the Douglas Mental Health University Institute in Montreal [Beaudry, 2007]. GUISPRO allows the user to select specific processing algorithms of the Montreal Neurological Institute (MNI) Brain Imaging Toolbox [Neelin, 1992] and the corresponding parameters and models to be applied to an according file or a whole folder of files in a graphical user interface. Preprocessing steps were as follows: First, the N3 algorithm was used to apply non-parametric non-uniform intensity normalization [Sled et al., 1998]. This step corrects for artifacts due to smooth signal intensity variations across images, also known as radio frequency inhomogenites. This preprocessing step improves the accuracy of anatomical analysis techniques such as tissue classification and cortical

surface extraction. In the next step Automated Linear Registration (AUTOREG) was used [Collins et al., 1994] to linearly register images to an average MRI brain model (n = 152) aligned with the Talairach stereotaxic coordinate system [Talairach & Tournoux, 1988]. Initially this method creates the transformation matrix of the alignment of images and co-planar, stereotaxic brain atlas. After recovering the transformation matrix images are resampled along new spatial dimensions with new

Mapping (ICBM). Finally images were normalized for intensity across the whole brain.

voxel positions to the 1mm template of the International Consortium for Brain

Assessment of Hippocampal Volume

Coded imaging data was analyzed blindfolded. Regional morphometric analyses were performed using MNI DISPLAY [MacDonald, 1996]. This manual segmentation software allows simultaneous real-time viewing and voxel labeling on sagittal, coronal, and horizontal planes (see Figure 1). Following the protocol as it was described by Pruessner and colleagues [Pruessner et al., 2001], the hippocampus was labeled as follows: Starting DISPLAY in tc-shell, brain color was set to gray, label opacity to 0.3. The left hippocampus was labeled blue; the right hippocampus was labeled green. Brush size was 0.5. The contrast between gray matter and cerebro-spinal fluid (CSF) was set using the lateral ventricle on the level of the hippocampal tail, where the lateral ventricle is not yet separated into body and inferior horn. The contrast was set so that the choroids plexus was clearly distinguishable from CSF within the lateral ventricle, coming from high brightness. One layer that was most probably an intersection layer was taken as a reference layer, i.e. that there was a clear distinction between gray matter and CSF at this point. The contrast between gray matter and white matter was set using the fronto-temporal junction (FTJ) as described by Pruessner [Pruessner et al., 2002]: the value of the voxel with the highest intensity within the anterior commissure minus 10% was taken as threshold for eight continuous voxels in the region where the FTJ was expected.

By convention a layer could be horizontal, vertical or diagonal. In general, at the transition of one type of matter to the other, one layer of matter that was to be painted was excluded as security layer to account for partial volume effects. However this rule was not applied for black spots within the hippocampus. Single black spots, i.e. spots that were not visible in at least two consecutive layers in the view that was used to paint, were included. Dark spots within the hippocampus (dark gray or black) that continued over at least two adjacent layers (depending on which view one was painting in, i.e. coronal or horizontal) were considered to be atrophy. In doubt no explicit security layer was taken, but the decision to label a voxel or not rather followed the overall visual impression of the dark spots and their surroundings: It was always the main goal to follow the anatomy; that meant for example the exclusion of the darkest spots where the ventricle or cistern were assumed to be. Hence, black spots and all dark spots that represented the anatomical course of an according structure were excluded. Although straight lines were preferred, especially were labeling followed help lines, because the resolution would not allow to determine the real anatomical border in question, the main goal was to follow the exact borders of gray matter and thereby try to trace the real shape; in doubt the security layer was left out. At the end of the procedure the so far labeled hippocampus was smoothed, i.e. corrections were applied to get an as homogenous and anatomical plausible shape as possible. Therefore, this step mainly consisted of checking for mutual plausibility between the single views. Hence, all three views were consulted simultaneously. A change was made, if it seemed plausible in at least two views.

In detail: The tail of the hippocampus (HT) was labeled in the coronal view until it descended into the body of the hippocampus (HB). The labeling started at the transition between HT and HB and went on posteriorly. Posteriorly the first appearance of ovoid mass of gray matter inferiomedially to the trigone of the lateral ventricle (TLV) in the coronal view mowing anteriorly marked the posterior border. Laterally the TLV was considered the border of the HT: Two rows of gray matter were excluded for TLV and caudate nucleus where this seemed appropriate. Medially the white matter formed the border of the hippocampus. Superomedially the focus was on the exclusion of the Andreas-Retzius gyrus (ARG) and of the crux of the fornix: This was reached by the mentioned procedure of moving forward to where the body was clearly visible and than labeling back as to reach consistency, i.e. to avoid big jumps in the HT. Medially the border normally could be detected very well. Additionally for the purpose of consistency the cursor was set one layer over the superior border in one slice. Then, moving posteriorly, the cursor would mark the superior border of the next

coronal slice.

The HB was labeled in the coronal view, too, until the uncal recess of the head of the hippocampus (HH). Inferiorly the white matter band marked the border. Here a security layer was taken, if the white matter was not visible. Superiorly one or two layers of the white matter (fimbria) were included. In addition one gray matter layer superiorly to the fimbria was included, if existent. Medially a straight line at a 45 angle from the most visible inferiomedial part of the HB medially to the cistern was drawn or the course of gray matter was followed where this seemed more adequate. One gray matter layer was taken as security layer to the cistern. Special emphasis lied on the exclusion of the subiculum. Laterally the lateral ventricle or the caudally adjacent white matter served as a border. If the ventricle was not visible itself, one gray matter layer was excluded instead.

The HH was painted in the horizontal view. Anteriorly the uncal recess of the inferior horn of the lateral ventricle (IHLV) functioned as boundary: Either the IHLV itself was visible anteriorly, then this was the anterior boarder. If the IHLV was only visible laterally, a horizontal layer was labeled to the cistern starting from the most anterior part of the IHLV. Medially this line was smoothed to already labeled matter. The IHLV consisted of two rows of gray matter, where the IHLV was not itself visible. Another orientation for the anterior border was the alveus. The superiorly border was checked for in the sagittal view, after horizontal painting was finished. Also here the uncal recess of the IHLV and the alveus formed the corresponding border. The inferior and medial boundaries where found analog to the procedure for the HB. Finally the uncal recess of the IHLV was used again to define the lateral border. Smoothing the form started in the sagittal view, continued in the coronal and ended in the horizontal view, always consulting all three views simultaneously. Omissions within the hippocampus where kept and not filled in.

Reliability Assessment

The reliability of the manual segmentation method has been described elsewhere [Pruessner et al., 2000]. The method was trained on ten fully preprocessed datasets of the MNI, which had been segmented by several raters before. Each of these scans was labeled twice. Before the work on the actual data started labels were evaluated by the

creation of probability maps to check for plausibility, quality and consistency. Internal validation of the consistency of the labeling took place after finishing the real data as well: A paired-sample t-test resulted in a correlation of r (35) = 0.858, p < 0.01, taken left and right hippocampal volume as paired variables. As left and right hippocampal volumes normally are strongly correlated this value served as indicator for the plausibility of the labeling. Additionally a scatterplot with right and left hippocampal volume as variables was used to determine extreme values. The labelings of subjects with extreme values were examined again to make sure they were adequate. Finally, the first supervisor of this study revised the medial part of the HT in each labeling, as this was the most problematic detail of the whole labeling process.

Voxel-Based Morphometry

Voxel-Based Morphometry was used to quantify localized gray matter density in the whole brain [Ashburner & Friston, 2000]. All structural images were converted into MINC-file format as described above. The previous manual segmentation made sure that each individual scan was visually inspected to ensure image quality and to check for abnormalities. Images were transferred to a server of the Brain Imaging Center of the MNI at McGill University. Additionally to the prior mentioned preprocessing steps tissue classification was conducted using the INSECT algorithm written by Alex Zijdenbos at the MNI. INSECT is an algorithm for automatic tissue-classification and therefore separates a structural MRI into its three tissue types: white matter, gray matter, and CSF [Collins & Evans, 1999, Evans et al., 1996, Zijdenbos et al., 1998]. Briefly, INSECT relies on an artificial neural network classifier, which labels each voxel based on the MRI signal in each input MRI volumes. The classifier was trained for each brain volume by providing it with the coordinates of voxels that have a minimum likelihood of 90% for belonging to one of the target tissue classes. The algorithm resulted in classified volumes of gray matter, white matter and CSF. After classification, the images were segmented so that only one tissue type appeared. A cortical surface was then created for each volume using an according algorithm of the MNI Brain Imaging Toolbox. Using the cortical surface, the skull and the dura were removed from the brain so that they did not interfere with the data. It should be noted that the cerebellum was not masked in the MRI volumes during these analyses

and, therefore, differences in overall gray matter were analyzed. After the according binary mask of voxels of the matter of interest was extracted from the classified image, this mask was smoothed using a Gaussian kernel of 10 mm full-width half-maximum (fwhm) in each image. A Gaussian kernel gives a weighted average of tissue density in a defined area surrounding a selected voxel, thus increasing signal-to-noise ratio. The voxel values in the resulting blurred matter masks are referred to as matter density. Smoothing converts existing data into a range of continuous data. This is required for the statistical procedures in VBM, which are based upon Gaussian random field theory. Furthermore, smoothing reduces the effect of individual variation in the exact location of gyri and sulci. It also reduces the number of comparisons for the regression analysis applied later on. It weights the signal at each voxel according to the signal in neighboring voxels, thereby reflecting the amount of gray matter within the smoothing kernel, i.e. its regional density or concentration. And it increases the validity of the Gaussian assumption, making the false positive rates more accurately determined [Watkins et al., 2001]. In balanced designs, provided the data are smoothed with a 4-mm FWHM kernel, non-normality is sufficiently attenuated to render the tests valid. Conventional group comparisons appear to be robust and remain valid even without smoothing [Salmond et al., 2002]. The average of the original corrected scans as well as the average of the classified gray matter to be used as a mask was computed using the MNI minctools. The minctools were used as well to choose voxels in the mask, which do not have intensity values below 0.1, i.e. anything above this value was left in the mask. Peaks and clusters were computed using the Find Peaks plug-in of NeuroLens and the respective thresholds. Thresholds were computed using Keith Worsleys frmistat (matlap toolbox) [Worsley et al., 2002]. Results were viewed with MNI Register and NeuroLens.

Statistical Analysis

Statistical analyses on the manually segmented volumes of the hippocampi were conducted using the Statistical Package for Social Sciences software (version 11.0.4, Mac OS X) [SPSS-Inc., 2005]. This included the computation of two- and three-factor mixed-design analyses of variance (ANOVA), partial correlations, descriptive group statistics and frequencies and the creation of scatterplots and graphs.

VBM analyses were performed with Glim Image, a program developed at the MNI [Golestani et al., 2002, Paus et al., 2001, Pruessner et al., 2001, Tisserand et al., 2004, Watkins et al., 2001. Glim image is designed for performing Voxel Based Morphometry, i.e. it examines the changes in segmented tissue matter (white matter, gray matter, CSF) as it relates to a linear model. The smoothed density maps were used to localize differences in tissue density, i.e. the gray matter maps were correlated with group membership (meditator vs. non-meditator), or change in breathing rate in case of meditators respectively, on a voxel-by-voxel basis using a linear regression model, yielding according t-maps. The linear regression analysis was applied to the individual voxels of all subjects. In sum: This analysis is conducted using the general linear model to compare the density of gray matter in e.g. two according groups, in order to identify differences in the concentration of gray matter that are related to the specific variables under study. For example the subjects corresponding group acts as independent variable, and the MRI image signal intensity of each voxel acts as a dependent variable in the regression. The output of this method is a statistical map that demarcates regions in which there is a significant difference in the concentration of gray matter between compared groups [Ashburner & Friston, 2000]. In the difference images, positive voxel values at one specific location indicated that at this location, the group with the higher value in the independent variable has a higher amount of gray matter than the group with the lower value and vice versa. Thresholds for the t-statistics were calculated based on the according sample size and the resulting degrees of freedom, a voxel size of 1 mm^3 , smoothness of 10 mm, a volume of interest of 2,523,032 voxels, and a significance level

of P < 0.005, corrected for multiple comparisons [Worsley et al., 1996].

Results

Manual Segmentation

Using the General Linear Model for an analysis of variance, a repeated measurement analysis with left and right hippocampal volume of each participant as within-subject factor and group membership as between-subject factor showed a trend towards meditators having larger hippocampal volumes than non-meditators $F_{1,33} = 2.263, p = 0.142$, two-factor $(group \times hemisphere)$ mixed design ANOVA). Looking at the data descriptively (see Figure 2) indicated a clear shift between both groups, i.e. the group of meditators had a tendency to higher hippocampal volumes. Furthermore this inspection allowed spotting an outlier within the control group. Performing the same analysis as described before with age as covariate and the exclusion of the outlier resulted in significantly higher hippocampal volume for meditators in comparisons to non-meditators $(F_{1,31} = 4.239, p = 0.048,$ two-factor $(group \times hemisphere)$ mixed design ANOVA).

Table 2: Descriptive statistics of hippocampal volume of the whole sample.

	N	Min	Max	Mean	SD
Right hippocampus (mm^3)	35	3,572	5,972	4,483.74	542.257
Left hippocampus (mm^3)	35	3,346	5,410	$4,\!429.63$	492.780

Notes: N = sample size, Min = Minimum, Max = Maximum, SD = Standard Deviation.

But as there was no reason to exclude this outlier, because it was still within the range of three standard deviations (see *Table 2*) and no additionally information was available, e.g. certain personality data, that would have justified carrying out such exclusion, results still had to be considered insignificant. And as it seemed even further indicated to check for the influence of whole-brain volume as well, the results so far could not be taken for granted anyway.

As speculated, testing for the influence of whole-brain volume (as additional covariate) demonstrated modified result, i.e. a decreased level of significance in both cases: with $(F_{1,31} = 1.657, p = 0.207, \text{ two-factor } (group \times hemisphere) \text{ mixed design}$ ANOVA) as well as without the outlaying control $(F_{1,30} = 3.042, p = 0.091, \text{ two-factor} (group \times hemisphere) \text{ mixed design ANOVA}).$

Although controls and meditators were matched for gender, the role of this factor had to be examined as well, because it was observed before in the case of age as



Figure 1: View on MNI DISPLAY.

Notes: DISPLAY is a program originally designed to display and manipulate three-dimensional objects, mainly human cortical surfaces and sulcal curves. It has since evolved to include MRI and PET volume display and manipulation and a variety of other features. The user interface is a non-standard menu oriented system.

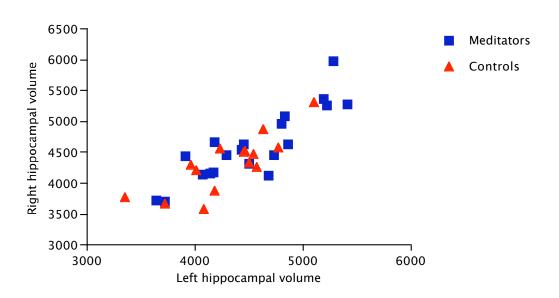


Figure 2: Relationship between left and right hippocampal volume.

Notes: scatterplot showing right hippocampal volume as a function of left hippocampal volume (in mm^3) for each participant. Meditators are shown in blue, controls in red.

a covariate that although the groups were matched for this factor, controlling for it could alter the results in the dimension of several cents. Furthermore it could have been possible to find effects of gender on the hemispheres or on the interaction group by hemisphere. It turned out that this analysis also could not reach significance $(F_{1,29} = 1.126, p = 0.297, \text{ three-factor } (group \times gender \times hemisphere) \text{ mixed design}$ ANOVA, covariates: age and whole-brain volume). Thus, there was no significant effect of group on left or right hippocampal volume. Also, there was no interaction effect of group by hemisphere $(F_{1,29} = 0.464, p = 0.501)$, and no repeated measures effect of hemisphere $(F_{1,29} = 0.168, p = 0.685)$.

But as there was a 9% difference between the two- and three-factor analysis, this result pointed to an interesting possible direction of further analysis, namely the examination of males and females in isolation: The main results of this analysis are illustrated in *Figures 3* to 7.

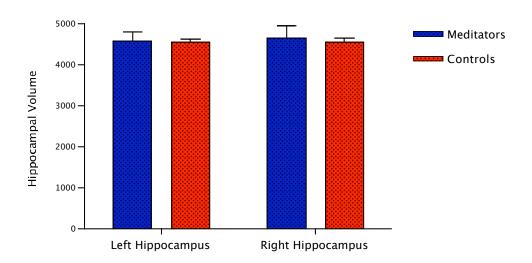


Figure 3: Hippocampal volume in female meditators and controls. Notes: Mean left (1) and right (2) hippocampal volume (in mm^3) in female meditators and controls: meditators are distinct from controls in the left hippocampus by only 0.4 % and about 2 % in the right hippocampus (left hippocampus: t(10) = 0.066, p = 0.949, 2-tailed; right hippocampus: t(10) = 0.246, p = 0.811, 2-tailed; independent samples t-test, variance homogeneity assumed).

In women the analysis was far away from being significant $(F_{1,8} = 0.075, p = 0.791, \text{ two-factor } (group \times hemisphere) \text{ mixed design ANOVA},$ covariates: age and whole-brain volume). Rather there tended to be no mentionable difference in the hippocampal volume of meditating women and their non-practicing counterparts. However, looking upon the male sample the trend towards a significant

difference regarding hippocampal volume in meditators and controls was still visible and stable ($F_{1,19} = 1.931, p = 0.181$, two-factor ($group \times hemisphere$) mixed design ANOVA, covariates: age and whole-brain volume).

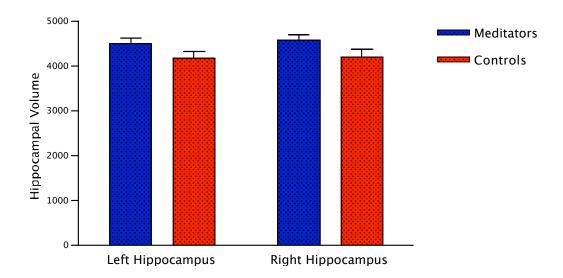


Figure 4: Hippocampal volume in male meditators and controls. Notes: Average left (1) and right (2) hippocampal volume in male meditators and controls (in mm^3): meditators differ from controls in the left hippocampus over 8 % and about 9 % in the right hippocampus (left hippocampus: t(21) = 1.579, p = 0.129, 2-tailed; right hippocampus: t(21) = 1.808, p = 0.085, 2-tailed; independent samples t-test, variance homogeneity assumed).

Men and women did not differ significantly in left or in right hippocampal volume (left hippocampus: t(33) = -1.248, p = 0.221, 2-tailed; right hippocampus: t(33) = -1.038, p = 0.307, 2-tailed; independent samples t-test, variance homogeneity assumed). The same held true for the comparison between female and male meditators (left hippocampus: t(18) = -0.342, p = 0.736, 2-tailed; right hippocampus: t(18) = -0.266, p = 0.794, 2-tailed; independent samples t-test, variance homogeneity assumed), as well as for female and male controls (left hippocampus: t(13) = -1.719, p = 0.109, 2-tailed; right hippocampus: t(13) = -1.476, p = 0.164, 2-tailed; independent samples t-test, variance homogeneity assumed). In every single case women had the larger hippocampus.

Voxel-Based Morphometry

The additionally conducted whole-brain analysis via VBM resulted in some interesting and even surprising results (see *Table 3*): Regarding the whole sample, non-meditating

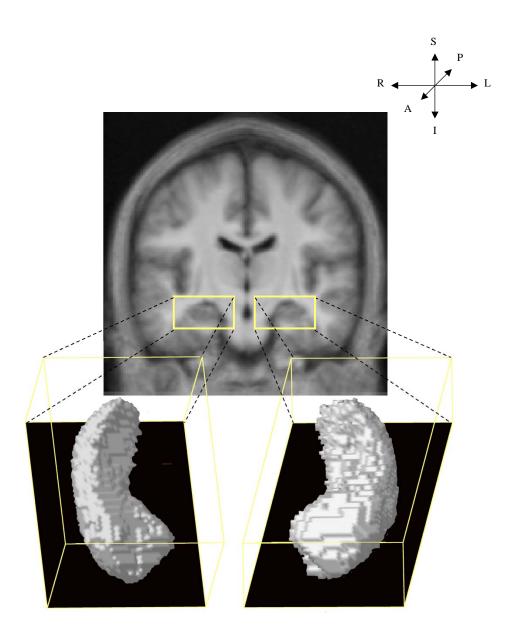


Figure 5: Hippocampal volume in male meditators.

Notes: Antero-superior view on left and right average label of hippocampal volume in male meditators (A: anterior, P: posterior, L: left, R: right, S: superior, I: inferior).

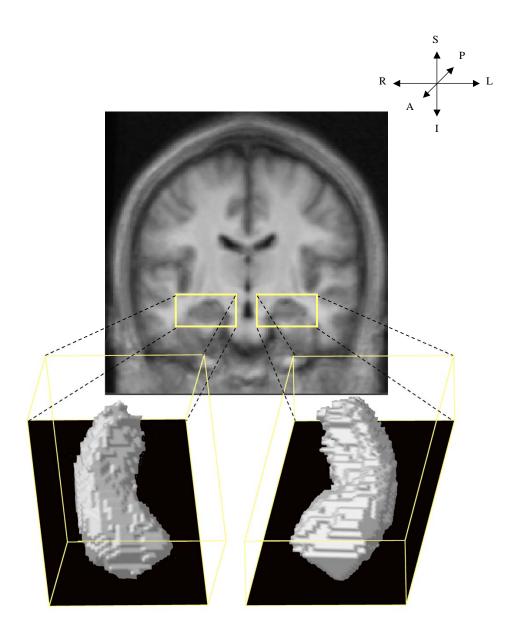


Figure 6: Hippocampal volume in male controls.

Notes: Antero-superior view on left and right average label of hippocampal volume in male controls (A: anterior, P: posterior, L: left, R: right, S: superior, I: inferior).

participants had significant higher gray matter concentration in comparison to practioners in the right rectal gyrus (x=7, y=18, z=-23; 7,101 voxels, p<0.01). The curious thing however were the results of an a-priori region-of-interest (ROI)-analysis testing for the regions Lazar [Lazar et al., 2005] reported before (in general all a-priori ROI-analyses conducted here were directed to regions Sara Lazar reported previously, because up to now her study is the only relevant anatomical study existing - functional studies were not considered): In the right superior frontal gyrus (x=28, y=61, z=3; 966 voxel, p=0.0120), as well as in the left superior temporal gyrus (x=-28, y=5, z=-42; 2,075 voxel, p=0.0446), there was a significant difference between the groups, but in the directly opposite direction that the researchers in Boston found. Thus, in these regions as well, controls had higher gray matter density than meditators. This result was even more startling, if one kept in mind that the current study used Sara Lazar's data.

But looking at the negative t-values, i.e. searching for brain regions, where meditators had higher gray matter density than controls, an a-priori ROI-analysis unveiled two regions that were found in the original study as well: The left postcentral gyrus (x = -31, y = -31, z = 74; 840 voxel, p = 0.0175) and the right superior frontal gyrus (x = 17, y = 66, z = 26; 2,286 voxel, p = 0.0365). The fact that the right superior frontal gyrus contained regions of higher gray matter concentration for each of the groups already relativized the possible apprehension that both studies could contradict each other. Rather it pointed to the fact that on the one hand the applied morphological methods might have different levels of accuracy (on a rather crude overall resolution), and on the other hand that the brain regions in question are so large and heterogeneous that it is well imaginable that there might be different effects of the same factor within one region. A-posteriori there was one brain region with significant differences in gray matter density that was not reported before: The left fusiform gyrus (x = -39, y = -64, z = -6; 497 voxel, p = 0.0448, see Figure 8).

Trying to get an even more detailed picture about the brain regions, which are shaped by meditation, meditative experience was used as first regressor variable in another voxel-wise analysis within the group of meditators (see *Table 4*). Because the change in breathing rate as mentioned before is one of the best and most objective indicators for meditative experience (Lazar et al., 2005), this biometric measure served

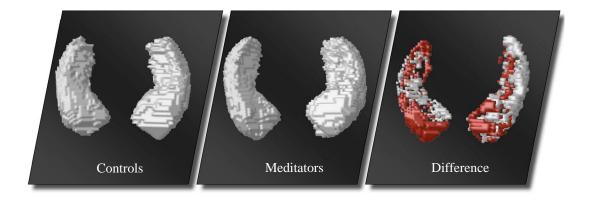


Figure 7: Comparison of hippocampal volume in male meditators and controls. Notes: Difference in hippocampal volume between male controls and male meditators observed on the level of direct visual-descriptive comparison: Difference figure shows regions where in meditators there was a hippocampal labeling with a probability of p=1.0 while in controls p was smaller than 1.0 (red) and vice versa (gray). It can be noticed that meditators show an increaded volume in the hippocampal head compared to controls, especially in the right hippocampus.

Table 3: Relationship between gray matter density and group membership.

Cortical Region	BA		High	est Pea	k	Cl	uster
		X	у	${f z}$	t-value	Size	p-Level
$Positive \ Association$							
Right Rectal Gyrus	R11	7	18	-23	3.81	7,101	< 0.01
Right Superior Frontal Gyrus*	R10	28	61	3	4.28	966	0.0120
Left Superior Temporal Gyrus*	L38	-28	5	-42	2.86	2,075	0.0446
Negative Association							
Left Fusiform Gyrus	L19	-39	-64	-6	-5.03	497	0.0448
Left Postcentral Gyrus*	L3	-31	-31	74	-3.35	840	0.0175
Right Superior Frontal Gyrus*	R10	17	66	26	-2.51	2,286	0.0365

Notes: Size in mm^3 , N = 35 (meditators vs. controls); controlled for gender, age and whole-brain volume; cluster-t-threshold = 3.35, cluster-size-threshold = 1,190 mm^3 , p = 0.05, corrected for multiple comparisons; "*": a-priori hypothesis: cluster-size-threshold: 375 mm^3 , BA = Brodmann Area.

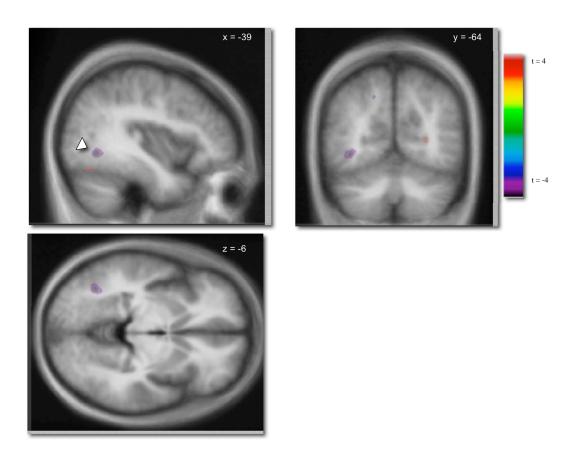


Figure 8: Gray matter density in the left fusiform gyrus. Notes: Higher gray matter density for meditators in comparison to control subjects in the left fusiform gyrus: statistical t-map was overlaid on the average brain of the sample (t-map shows differences in gray matter density at each gray matter voxel of the brain; all voxels with a t-value > 4 and < -4 are shown). White arrow points to the region in question.

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Cortical Region	BA		Highest Peak		Cluster		
		X	У	\mathbf{Z}	t-value	Size	p-Level
Positive Association							
Left Precentral Gyrus	L4	-63	-13	38	5.09	27,587	< 0.01
Right Postcentral Gyrus	R3	59	-17	56	4.65	$24,\!378$	< 0.01
$Negative \ Association$							
Left Superior Frontal Gyrus	L6	-9	23	69	-6.85	1,512	< 0.01
Right Posterior Cingulate	R30	18	-54	15	-5.08	1,441	< 0.01
Left Posterior Cingulate	L30	-17	-56	14	-4.34	2,301	0.0497

Table 4: Relationship between gray matter density and change in breathing rate.

Notes: N = 20 (meditators); controlled for gender, age and whole-brain volume; cluster-t-threshold = 3.58, cluster-size-threshold = $1,100~mm^3$, p = 0.05, corrected for multiple comparisons; "*": a-priori hypothesis: cluster-size-threshold: $314~mm^3$, BA = Brodmann Area.

as predictor variable. Less experienced practioners had higher gray matter density in the left precentral (x = -63, y = -13, z = 38; 27,587 voxel, p < 0.01) and the right postcentral gyrus (x = 59, y = -13, z = 38; 24,378 voxel, p < 0.01).

Negative t-values, i.e. regions where more experienced practioners had a higher concentration of gray matter compared to meditators with less experience, were found in the left superior frontal gyrus (x = -9, y = 23, z = 69; 1,512 voxel, p < 0.01, see Figure 9), the right (x = 18, y = -54, z = 15; 1,441 voxel, p < 0.01, see Figure 10) and the left posterior cingulate (x = -17, y = -56, z = 14; 2,301 voxel, p = 0.0497).

As the results of the manual segmentation showed that only in men an effect of meditational practice on hippocampal volume was found, it seemed indicated to analyze men and women separately in a whole-brain voxel-wise analysis, too. Looking especially to all regions previous reported by Lazar [Lazar et al., 2005] and the hippocampal formation as a-priori regions of interest, analyses revealed following surprising results in men (see *Table 5*): Nearly all ROI-analyses found higher gray matter density for controls in the areas previously reported by Sara Lazar. There was one region in the controls that was significant a-posteriori: the right superior temporal gyrus (x = 68, y = -42, z = 20; 2,903 voxel, p = 0.0138), a region, for that Lazar also reported higher cortical thickness in meditators than in controls. Male meditators showed higher gray matter concentration than non-practitioners in the right inferior temporal gyrus (x = 62, y = 25, z = 6; 13,425 voxel, p = 0.0109, see *Figure 11*) and

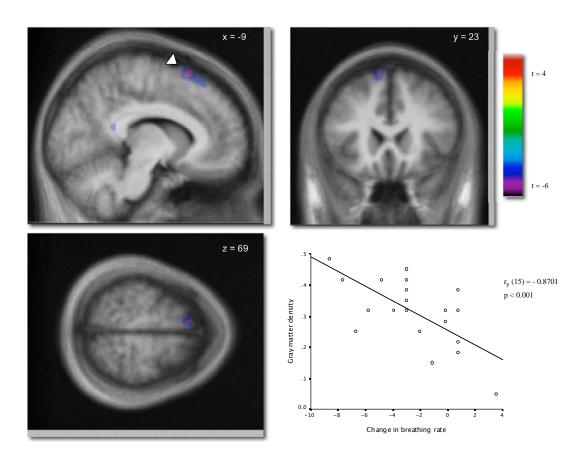


Figure 9: Gray matter density in the left superior frontal gyrus.

Notes: Higher gray matter density for more experienced meditators in the left superior frontal gyrus compared to less experienced practitioners: statistical t-map was overlaid on the average brain of meditators in the sample (t-map shows differences in gray matter density at each gray matter voxel of the brain; all voxels with a t-value > 4 and < -4 are shown). White arrow points to the region in question. scatterplot depicts the gray matter density in the left superior frontal gyrus (x = -9, y = 23, z = 69) as a function of the change in breathing rate for each meditator. A partial correlation between gray matter density and change in breathing rate controlling for age,

gender and whole-brain volume revealed a negative correlation coefficient: $r_p(15) = -0.8701(p < 0.001)$.

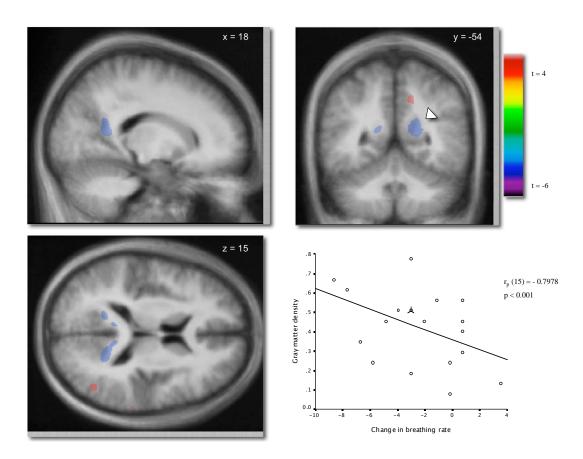


Figure 10: Gray matter density in the right posterior cingulate.

Notes: Higher gray matter density for expert-meditators in the right posterior cingulate compared to less experienced meditators: statistical t-map was overlaid on the average brain of sample-meditators (t-map shows differences in gray matter density at each gray matter voxel of the brain; all voxels with a t-value > 4 and < -4 are shown). White arrow points to the region in question. scatterplot depicts the gray matter density in the right posterior cingulate (x = 18, y = -54, z = 15) as a function of the change in breathing rate for each meditator. A partial correlation between gray matter density and change in breathing rate controlling for age, gender and whole-brain volume revealed a negative correlation coefficient: $r_p(15) = -0.7978(p < 0.001)$.

Table 5: Gray matter density and group membership in men.

BA	Highest Peak			Cluster		
	X	У	\mathbf{z}	t-value	Size	p-Level
R13	46	5	5	4,85	250	0.0395
s R22	68	-42	20	3.88	2,903	0.0138
R46	46	46	4	4.07	1,935	< 0.01
L41	-48	-28	16	3.70	1,637	< 0.01
L20	-48	-3	-44	4.22	19,926	< 0.01
R30	31	-62	7	3.28	4,624	< 0.01
R45	62	25	6	-2.80	$13,\!425$	0.0109
L40	-56	-31	57	-4.07	2,648	0.0283
	R13 s R22 R46 ' L41 L20 R30	R13 46 s R22 68 R46 46 c L41 -48 L20 -48 R30 31	x y R13 46 5 s R22 68 -42 R46 46 46 c L41 -48 -28 L20 -48 -3 R30 31 -62 R45 62 25	x y z R13 46 5 5 s R22 68 -42 20 R46 46 46 4 4 L41 -48 -28 16 L20 -48 -3 -44 R30 31 -62 7	x y z t-value R13 46 5 5 4,85 s R22 68 -42 20 3.88 R46 46 4 4.07 4 L41 -48 -28 16 3.70 L20 -48 -3 -44 4.22 R30 31 -62 7 3.28	x y z t-value Size R13 46 5 5 4,85 250 s R22 68 -42 20 3.88 2,903 R46 46 4 4.07 1,935 c L41 -48 -28 16 3.70 1,637 L20 -48 -3 -44 4.22 19,926 R30 31 -62 7 3.28 4,624 R45 62 25 6 -2.80 13,425

Notes: N = 23 (men); controlled for age and whole-brain volume; cluster-t-threshold = 3.51, cluster-size-threshold = 1,127 mm^3 , p = 0.05, corrected for multiple comparisons; "*": a-priori hypothesis: cluster-size-threshold: 332 mm^3 , BA = Brodmann Area.

a-priori in the left postcentral gyrus (x = -56, y = -31, z = 57; 2,648 voxel, p = 0.0283).

Although the sample size was rather small the same analysis was also conducted for women (see *Table 6*). Again, all the a-priori analyses found higher gray matter density for controls in areas, which Sara Lazar reported higher cortical thickness in meditators for. But also a-posteriori analyses found corresponding areas contrasting Lazars findings: There was higher gray matter density in controls in the right middle temporal gyrus (x = 46, y = 12, z = -35; 242 voxel, p = 0.0476), the left middle frontal gyrus (x = -35, y = 45, z = 11; 4,338 voxel, p = 0.0117) and the left superior frontal gyrus (x = -37, y = 35, z = 31; 21,858 voxel, p < 0.01).

Meditating women had gray matter concentration in the left thalamus that was almost significantly higher than in female controls (x = -2, y = -27, z = 0; 950 voxel, p = 0.0593, see Figure 12). ROI-analyses found higher great matter density in female meditators also in the left precentral gyrus (x = -31, y = -13, z = 64; 310 voxel, p = 0.0295), the left fusiform gyrus (x = -38, y = -64, z = -7; 236 voxel, p = 0.0498), the left postcentral gyrus (x = -38, y = -27, z = 70, 972 voxel, p = 0.0170) and the right superior frontal gyrus (x = 30, y = 55, z = 37; 878 voxel, p = 0.0214).

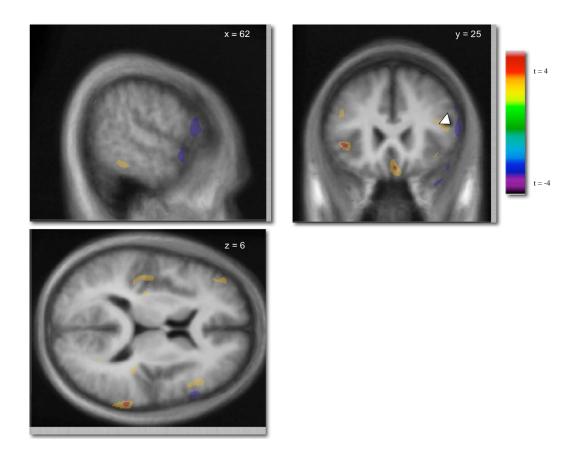


Figure 11: Gray matter density in the right inferior temporal gyrus. Notes: Higher gray matter density for male meditators in the right inferior temporal gyrus in comparison to male control subjects: statistical t-map was overlaid on the average sample male brain (t-map shows differences in gray matter density at each gray matter voxel of the brain; all voxels with a t-value > 2.4 and < -2.4 are shown). White arrow points to the region in question.

Table 6: Gray matter density and group membership in women.

Cortical Region	BA	A Highest Peak			Cluster		
		X	У	${f z}$	t-value	Size	p-Level
Positive Association							
Right Superior Frontal Gyrus*	R10	31	58	-4	8.48	646	< 0.01
Right Middle Frontal Gyrus*	R9	33	26	30	6.78	401	0.0168
Right Posterior Cingulate*	R29	7	-49	8	6.14	357	0.0218
Right Middle Temporal Gyrus	R21	46	12	-35	11.88	242	0.0476
Left Middle Frontal Gyrus	L10	-35	45	11	5,97	4,338	0.0117
Left Superior Frontal Gyrus	L9	-37	35	31	5,97	21,858	< 0.01
Right Insula*	R13	36	10	-6	4.27	3,390	0.0334
Negative Association							
Left Thalamus	-	-2	-27	0	-6.25	950	0.0593
Left Precentral Gyrus*	L6	-31	-13	64	-7.46	310	0.0295
Left Fusiform Gyrus*	L37	-38	-64	-7	-5.36	236	0.0498
Left Postcentral Gyrus*	L1	-38	-27	70	-4.79	972	0.0170
Right Superior Frontal Gyrus*	R9	30	55	37	-4.06	878	0.0214

Notes: N = 12 (women); controlled for age and whole-brain volume; cluster-t-threshold = 4.03, cluster-size-threshold = 973 mm^3 , p = 0.05, corrected for multiple comparisons; "*": a-priori hypothesis: cluster-size-threshold: 231 mm^3 , BA = Brodmann Area.

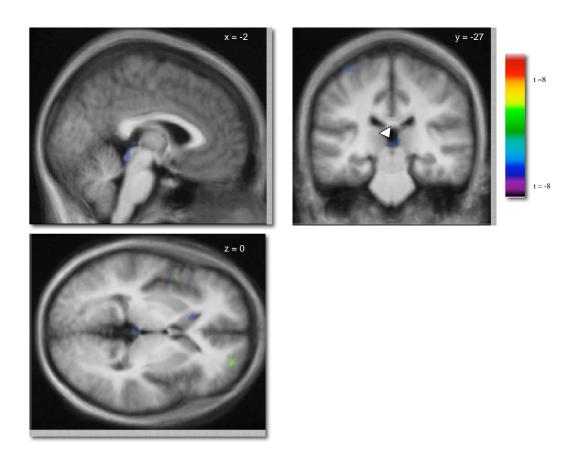


Figure 12: Gray matter density in the left thalamus. Notes: Higher gray matter density for female meditators in the left thalamus in comparison to female non-meditators: statistical t-map was overlaid on the average sample female brain (t-map shows differences in gray matter density at each gray matter voxel of the brain; all voxels with a t-value > 4 and < -4 are shown). White arrow points to the region in question.

Discussion

In this study the hypothesis was tested that meditative practice leads to increased hippocampal volume. For this purpose hippocampal volume of 20 meditators and 15 non-practicing controls was accessed by manual segmentation. Although not statistically significant there was a trend in meditators to have larger hippocampal volumes. A more specific analysis revealed that this trend was nearly exclusively driven by the male sample. Additionally whole-brain analyses were conducted that initially found higher gray matter density in the left fusiform gyrus when comparing meditators and controls. Expert meditators had higher gray matter concentration in the left superior frontal gyrus and posterior cingulate bilaterally compared to less experienced practitioners. There were also gender specific results: Meditating women had higher gray matter density in the left thalamus and men in the right inferior temporal gyrus, compared to their according control group.

Meditation and Gender Differences in Hippocampal Volume

The results of the manual segmentation of the hippocampal volumes in meditators and controls, although not significant, nonetheless show a clear trend to higher hippocampal volume in meditators. Thus, if the hypothesis that was derived in the introductory part of this thesis is believed to hold true, these findings validate the assumption that meditative practice alter stress-related symptoms by changing the morphology of the hippocampal formation. That opens a question on the next, more detailed level of explanation, namely how meditational practice brings about changes in the hippocampus. This was already outlined in the introduction: Meditative techniques are in general assumed to activate the prefrontal and cingulate cortex by willingly and actively intent to focus on a certain object or keep the mind in an only watching state [Frith, 1991, Pardo et al., 1991, Posner & Petersen, 1990]. The main support for this view comes from research exploring human attention: Here it t is assumed by some researchers that there are special brain networks that carry out the functions of attention. These include orienting to sensory stimuli, maintaining the alert state, and orchestrating volitional control. There is evidence that these networks have a certain degree of anatomical and functional independence, but that they also interact in many practical situations [Fernandez-Duque & Posner, 2001]. At this, the

brain network responsible for alerting / vigilance is assumed to consist of frontal and parietal cortical regions particularly of the right hemisphere. The orienting network in turn is said to consist of parts of the superior and inferior parietal lobe, frontal eye fields and subcortical areas such as the superior colliculus of the midbrain and the pulvinar and reticular nucleus of the thalamus

[Posner & Petersen, 1990, Posner & Rothbart, 2007]. Thus, although still relatively imprecise, the brain regions, which initially reflect the main characteristics of the meditative technique, as they were described above, can be identified.

Via the thalamic reticular nucleus the activation of prefrontal areas might lead to a reduced input into the superior parietal lobule (SPL) (see Figure 13). This deafferentation of the SPL during meditation may result in the stimulation of the hippocampus [Lou et al., 1999, Lou et al., 2005] via the glutamate system, because of the inverse modulation of the hippocampus in relation to cortical activity: Since the hippocampus is extensively interconnected with the prefrontal cortex, other neocortical areas, the amygdala, and the hypothalamus [Fuchs & Flugge, 2003], it is able to modulate and moderate cortical arousal and responsiveness [Redding, 1967]. At the same time the activation of the thalamus, as part of the attentional system responsible for orienting, might cause direct stimulation of the hippocampus by glutamate as well and would thereby enhance the stimulation of the hippocampus even more. This finally might lead to an increased hippocampal volume.

Basically, there are three different kinds of hippocampal plasticity: ongoing neurogenesis of the dentate gyrus, synaptogenesis under control of estrogens in the CA1 region [McEwen, 1999, Takagi et al., 2002] and dendritic remodeling caused by changing levels of exogenous glucocorticoids (steroid hormones) or excitatory amino acids in the CA3 region

[McEwen et al., 2001, McEwen, 2001, McEwen & Magarinos, 2001]. In all three forms of structural plasticity, there acts a synergy of excitatory amino acids and circulating steroid hormones [Fuchs & Flugge, 1998, McEwen et al., 2001]. This is indeed a rather complex area and the strong interdependency between the according neurotransmitters and the actions of steroid hormones complicate the case [McEwen, 1996]. But since most excitatory input in the hippocampus and cerebral cortex act upon dendritic spines, alterations in dendritic spine density or shape are most probably the

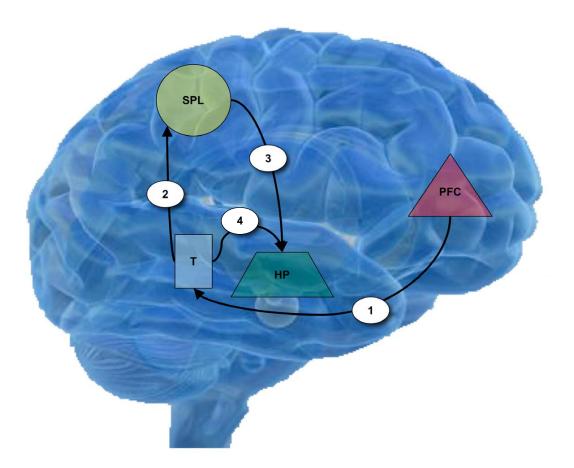


Figure 13: Overview over the proposed underlying mechanism.

Notes: PFC: Prefrontal Cortex; T: Thalamus; HP: Hippocampus; SPL: Superior parietal lobule. Initially the PFC is activated by the focusing of attention while meditative practice. This in turn activates the reticular nucleus of the T, particularly as part of the according attentional network (1). This again will lead to a deafferentation of the SPL (2). Decreased activity in this region could explain the altered perception of the self during meditation. The deafferentation of the SPL may lead to a stimulation of the HP via glutamate and Gamma-aminobutyric acid (GABA) systems respectively, because of the inverse modulation of the HP in relation to cortical activity (3). Additionally the hippocampus gets directly stimulated simultaneously by the thalamus via glutamate (4). This stimulation will lead to an increased hippocampal volume, because it induces dendritic tree growth via LTP.

morphological manifestations of changes in physiology or behavior and therefore also most probably the best explanation for increased hippocampal volume due to meditative practice. The links between spine plasticity and physiological responses have been best studied in the hippocampus in the context of long-term potentiation (LTP) [Gazzaley et al., 2002]. Hence, one activity-dependent modification within the hippocampus that could account for an increased hippocampal volume in meditators is LTP, a sustained increase in synaptic strength that is elicited by brief high frequency stimulation of excitatory afferents [Malenka, 1994]. Broadly speaking, this mechanism was found to involve a signal transduction cascade that includes release of glutamate and the activation of the NMDA glutamate receptors

[Heinemann et al., 1990, Miyamoto, 2006]. So, in the end, increased hippocampal

[Heinemann et al., 1990, Miyamoto, 2006]. So, in the end, increased hippocampal volume could account for reduced sensitivity to stress, because a larger hippocampal volume would mean a stronger inhibition of the human stress response system as deduced earlier [Heinemann et al., 1990, Miyamoto, 2006].

In terms of completeness, it is important to shortly address the issue of Neurotoxicity Hypothesis of cortisol versus Variability Hypothesis of hippocampal volume in this context: The Neurotoxicity Hypothesis states that lower self-esteem would result in higher levels of perceived stress. This would in turn cause a restricted regulation of the HPA-axis and thus create increased cortisol release over lifetime. Higher levels of cortisol would then in the end be the reason for the shrinkage of hippocampal volume due to the neurotoxic effects of cortisol. This is a plausible assumption. Still the idea that underlies this study is in favour of the Variability Hypothesis of hippocampal volume. This hypothesis assumes instead that the naturally occurring variability of hippocampal volume is the reason for different levels of self-esteem: In this view lower hippocampal volume leads to an impaired inhibition of the activity of the HPA-axis and hence the stress system is stimulated more often. More frequent and probably even higher increased cortisol levels in facing stressors over time will lead to higher levels of perceived stress and the believe that one is not able to handle stressful situations adequately. Thus, the feeling of control and competence as measured on common self-esteem-scales is reduced resulting in lower scores on these questionnaires [Pruessner et al., 2005]. The main argument for this second hypothesis is that hippocampal volume is as variable in young as in older

adults. Thus, the attribution of smaller hippocampal volume to the release of neurotoxic stress hormones over lifetime could in fact represent hippocampal volume determined early in life, i.e. pre-determined inter-individual differences in hippocampal volume in humans may determine the vulnerability to stress and for psychopathology throughout the lifetime [Lupien et al., 2007]. Relating this idea to the reasoning of the current study would lead to a slight adaptation of the Variability Hypothesis, insofar that the variability of hippocampal volume not only occurs naturally, but can be also due to experience inducing synaptic plasticity.

Because the reported findings regarding the brain networks, which constitute the human attentional system, are mainly found in the right hemisphere, the proposed mechanism underlying the increase in hippocampal volume due to meditative practice would not exclusively, but still essentially affect the right hemisphere. This would be a plausible explanation for the fact that the right hippocampus seems to be always larger, no matter in which analysis. Of course this conclusion is disputable, as there are findings that suggest that the right hippocampus is larger than the left in normal, healthy, right-handed subjects anyways

[Goncalves-Pereira et al., 2006, Li et al., 2007, Szabo et al., 2001]. But still one would have to explain this finding, and the described relationship between attention in general and the resulting stimulation of particularly the right hippocampus might point into the right direction.

At this point, it becomes clear that the reported outlier within the control group, that prevented the uncontrolled results from becoming significant, can be explained more easily. Because, if one regards meditation as a special kind of attentional training [Lazar et al., 2005] rather than an exclusive phenomenon that stands on its own, and its effects as embedded in the overall human attentional framework and not as meditation-specific, then one suddenly has a wide range of possible explanations at hand, why the control might be an outlier, for instance that he pursues a profession or simply a hobby that requires high concentrational skills and that would not be assessed in the sociodemographical screening, as he might be for example a surgeon, an air traffic controller or might practice distance shooting. The results of an only lately published study emphasize this strong connection between meditational practice and attentional training and furthermore might give an insight

into where exactly in the human attentional system meditation might unfold its effects: Applying a attentional-blink-paradigm researchers could show that meditative training could improve performance on a novel task that required trained attentional abilities. Particularly the role of meditation was seen in increased control over the distribution of limited brain resources [Slagter et al., 2007].

The most interesting finding in the manual analysis however, is the fact that

only in men the trend to larger hippocampi in practitioners can be observed, while in women meditative experience is not linked to higher hippocampal volume. Unfortunately there have not been many studies focusing on hippocampal volume in normal, healthy subjects. Research rather focused on patients with specific disorders or diseases, such as depression, mild cognitive impairment (MCI), post-traumatic stress disorder (PTST), schizophrenia, Alzheimers disease or epilepsy. But still there are some studies that give some insight into this issue: Several studies revealed that in normal, healthy samples there were no significant differences concerning the volume of the hippocampus among different age and gender groups [Goncalves-Pereira et al., 2006, Li et al., 2007, McHugh et al., 2007, Sullivan et al., 2005. If a gender effect was found, than women had larger hippocampi compared to men [Bigler et al., 1997]. The same trend can be seen in this study. In general rather variables like cerebral volume seemed to contribute to variance in hippocampal volume [Harding et al., 1998]. However, other studies found a negative correlation between mean total volume of the hippocampi and age in normal subjects, tough pointing to the phenomenon of regional selectivity of neuronal loss within the hippocampal formation in aging at the same time [Jack et al., 1998, Simic et al., 1997]. And yet another study could find a significant negative correlation with age for both left and right hippocampus. Interestingly enough in this study, the effect could only be found in men, but not in women [Pruessner et al., 2001]. These seemingly contradictory findings might be explainable, if one takes into consideration the sometimes very different techniques and protocols, which were applied to determine the volume of the hippocampal formation. As the last two mentioned studies used the most sophisticated methodology, it is assumed here, that there indeed exists an age-effect regarding hippocampal volume and furthermore that this effect is at least most prominent if not exclusively present in men. Thus, to summarize, there seems to

be no significant difference in hippocampal volume between men and women, and this study supports this opinion. The hippocampal formation in men however is subject to a decline with advancing age.

This assumption, that there are mechanisms that are distinct in men and women regarding brain morphology, seems to be even more feasible as gender-specific changes in volume of several brain structures have been reported elsewhere, too: E.g. researchers found that smaller right hippocampal volume underlied the basis for higher anxiety-related traits in both genders, whereas anterior prefrontal volume contributed only in females [Yamasue et al., 2007]. Even more interesting a study exploring the potential influence of gender on the morphology of temporal lobe structures in patients with schizophrenia found that the temporal lobe volume on the left was significantly smaller in male patients than in male comparison subjects. Female patients and female comparison subjects however demonstrated no significant difference in temporal lobe volume. Though this study could not find significant gender interactions for the hippocampal complex Bryant et al., 1999. Hence, generally speaking it seems that in different settings men tend to have a decline in brain volume, while women seem to stay unchanged. Gender differences were also shown in the pattern and number of correlations between the volume of the brain and its subregions and full-scale, verbal, and performance intelligence quotient (IQ) [Andreasen et al., 1993]. Researchers could actually show that the postnatal environment modulates the neurodevelopmental consequences of prenatal risk and that this effect is gender-specific, too Buss et al., 2007. Finally, only recently an fMRI experiment gave hints that there might be different underlying mechanisms in stress processing in women and men, because there were different functional neuronal activation patterns in men and women in response to a social stressor. Replicating earlier findings [Li et al., 2005] that study pointed into the direction of different stress-systems in men and women [Pruessner, 2006]. Especially this last finding might be counted as a strong argument for the possibility that meditation might effect the female brain quite differently to what happens in the male brain, because it has been shown earlier that the human stress response system and the possible mechanism underlying meditative practice are strongly interconnected.

Ultimately, the question remains what the reason for the observed

gender-differences might be. There are clues that point in the direction of differences in gene disposition; for example the apolipoprotein E epsilon4 genotype status appeared to have a greater harmful effect on gross hippocampal pathology and memory performance in women than in men [Fleisher et al., 2005]. But a more obvious solution might lie in the activity of certain hormones. The specific role of estrogen was already sketched: Researchers could find evidence for the essential role of endogenous hippocampal estrogen in hippocampal synaptic plasticity [Rune et al., 2006]. Maybe the strongest hint for this line of reasoning is the outcome of a study that could show that elderly women, who undertook estrogen replacement therapy (ERT) had larger right hippocampal volumes than women subjects not taking ERT and larger anterior hippocampal volumes than women subjects not taking ERT. These findings suggest a neuroprotective effect of estrogen [Eberling et al., 2003]. Following this idea in the context of the current study, the explanation for the reported findings could then look as follow:

Estrogen has a neuroprotective effect (without any further explanation this assumption is taken for granted here, because the cited study seems quite conclusive. Still there might be other possible interpretations of the given evidence, e.g. that it is rather the reduced testosterone-level that accounts for a reduced neurodegeneration). As women own estrogen in sufficient extent, their brain undergoes less natural degeneration until their menopause is finally reached. Because men only possess estrogen on a very low level, their brains run through stronger natural neuronal degeneration with advancing age and this process might start already in early adulthood [Gur et al., 2002]. Neuronal degeneration not only affects male and female brains in varying strength, but also in different areas [Cowell et al., 2007]. In men the hippocampus is one of the affected areas [Pruessner et al., 2001]. But there are processes that allow men to counteract this decline. One of these possible antagonists is meditative practice. Practicing meditation activates amongst other things specific attentional networks. This activation, if it is triggered regularly and for a certain amount of time, is able to stimulate the hippocampus in a certain way and thereby induce LTP in the hippocampal formation. This will finally lead to dendritic development and help to overcome the reduction of hippocampal volume due to natural degeneration.

And in fact, there is evidence for this argumentation from a VBM-study, in which it was examined how the regular practice of Zen meditation may affect the normal age-related decline of cerebral gray matter volume observed in healthy individuals: Meditators did not show a significant negative correlation of gray matter with age. Researchers concluded that these findings suggest that the regular practice of meditation may have neuroprotective effects [Pagnoni & Cekic, 2007]. And also Sara Lazar drew this conclusion from her cortical thickness study and stated that her results suggest that meditation might offset age-related cortical thinning [Lazar et al., 2005]. Whether it should be referred to neuroprotection or rather neuronal development is open at this point. Maybe it is even a matter of definition.

So in short: Female brains and especially female hippocampi are protected against neurodegeneration by high levels of estrogen within the female organism. Thus, hippocampal volume is quite stable over time. Nevertheless meditative practice might lead to slightly enhanced hippocampal volumes in women, which accounts for the small degree of natural degeneration that female hippocampi are still subject to. But as women are always close to a 100% so to say, this increase is rather limited. However, in men certain techniques, as meditative practices, might be able to bring about significant differences in hippocampal volume, when practitioners and non-practioners are compared. Because male hippocampi undergo a stronger degeneration, as they are missing the neuroprotective effects of estrogen, they have to make up for a greater gap to reach the 100% again. And that is why one would expect female hippocampi rather unchanged comparing meditating and non-meditating women, while there should be an increased average hippocampal volume in meditating men in comparison to male non-practitioners, because latter would still suffer from age-related, natural neurodegeneration. Furthermore one would anticipate that hippocampal volume in meditating men approaches the level of female hippocampal volume, but does rather not exceed it. And this is exactly would was found in this study.

As intuitive as this reasoning might sound, one has to keep in mind, that it is still highly speculative and within the scope of this study only an attempt to make sense of the reported findings. And one question stays unanswered right away, namely, why, although researchers could find differences in mechanisms regarding morphological changes in the brain of men and women, they could not find significant,

gender-specific differences in brain volumes. Concretely: Why is there evidence for an age-related decline in male hippocampi, and yet no significant difference in hippocampal volume between men in women, no matter which age group or which age-range is tested [Li et al., 2007, McHugh et al., 2007, Sullivan et al., 2005]?

Meditation and Its Effects on a Whole-Brain Scale

On the first sight the results of the VBM-analyses seem to be quite confusing and not conclusive. One might even be tended to question the results, as they could not really replicate the findings of Sara Lazar [Lazar et al., 2005], but even seem to contradict her findings, although both studies worked on the same data only using different methods. First of all it has to be mentioned here that all kinds of plausibility checks were applied to make sure that the results were not achieved by a mistake during statistical analyses or an error in the methodology. Especially the most obvious possible side of a mistake occurring, namely the coding of the subjects group membership, was reconsidered, but proofed correctly. Beyond these thoughts there is also a methodological issue: Although it is plausible to assume that cortical thickness analyses and VBM should yield comparable results when applied to the same set of data, the exact relation between the two methods still has to be addressed and remains open up to the present [Narr et al., 2005].

But the main reply seems to be that what rendered the results messy was mainly the inclusion of the a-priori ROI-analyses. Those analyses are suspect in the sense that they are rather unspecific, i.e. because the corresponding cluster-size thresholds are so small, clusters can be found all over the brain (cf. Figure 14).

One could object that it is still surprising that exactly the regions, where Lazar found higher cortical thickness in meditators, often were those regions, in which in this study controls had higher gray matter concentration. But this is simply because by definition only these regions were examined. Being moreover aware of the general limitations especially of VBM-analyses [Bookstein, 2001], only the most significant results should be taken into further consideration. Thus, if one considers exclusively the a-posteriori results there is not really a contradiction-potential any longer. On the contrary, quite interesting and also intelligible findings remain: Within the whole sample meditators had higher gray matter density in the left fusiform gyrus. Already

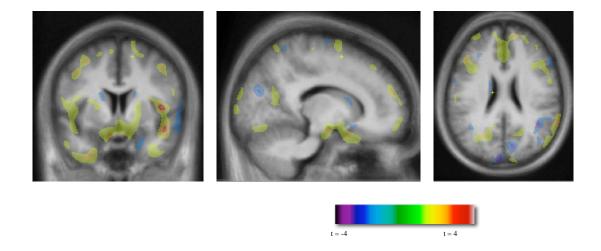


Figure 14: Example of cluster distribution in a ROI-analysis.

Notes: Taken from the VBM-ROI-analysis in men these pictures show how rather unspecific significant clusters can be found all over the brain, when the cluster-size becomes small.

in 1999 a PET-study could show that activity in the fusiform gyrus is associated with

visual imagery during relaxation meditation (Yoga Nidra) [Lou et al., 1999]. In the

first instance these results can obviously not be interpreted to be meditation-specific. But as also Lazar [Lazar et al., 2005] could find higher cortical thickness in the inferior occipito-temporal visual cortex in her study when testing for the role of meditative experience in the group of practitioners, now there seems to be some reason to believe that these areas are in fact involved and shaped in meditative practice. Some other more recent studies figured out some very interesting things about the fusiform gyrus: The fusiform gyrus is rather sensitive to attentional modulation [Tallon-Baudry et al., 2005], so that regular attentional training, such as some form of meditative practice, would indeed be able to modify the morphology of this region over time. This conclusion makes all the more sense, as it could be shown that there is a precise topographic relationship between parts of the fusiform gyrus and the pulvinar of the thalamus [Clarke et al., 1999]. Because this finding fits perfectly the earlier mentioned Newberg-Iversen-Model [Newberg & Iversen, 2003] and corresponding models of attention [Posner & Petersen, 1990], both of which were taken as a basis for this study. Furthermore the fusiform gyrus might even be approached directly in meditative practice: Researchers could demonstrate that there is a strong selectivity in distinct but adjacent regions in the fusiform gyrus for only faces in one region (the fusiform face area) and only bodies in the other (the fusiform body area)

[Peelen & Downing, 2005, Schwarzlose et al., 2005]. And as it is known that meditation brings about an altered sense of ones own body [Kabat-Zinn et al., 1985], the fusiform gyrus might actually be an area, where these changes might take place on a neuroanatomical level.

In this study meditative experience was associated with higher gray matter concentration in the posterior cingulate bilaterally and the left superior frontal gyrus. Most studies could not find any significant activity in the superior frontal gyri connected to meditation [Newberg et al., 2001]. But Lazar [Lazar et al., 2005] found increased cortical thickness in the right superior frontal sulcus. This result hinted to a possible role the superior frontal gyri might play for meditative experiences. The superior frontal gyri, especially on the left hemisphere, are actually cases of rather large and heterogeneous brain areas [Petrides & Pandya, 1999] so that to make any well-validated statements regarding this area must necessary involve a more detailed analysis. Hence, the present results should be considered as a guideline for future research. Nevertheless, a first preliminary attempt at an explanation should be permitted at this point: As researchers suggested that the left superior frontal gyrus is involved in higher levels of working memory processing (monitoring and manipulation) and remains oriented towards spatial cognition, although the domain specificity is not exclusive and is overridden by an increase in executive demand, regardless of the domain being processed [du Boisgueheneuc et al., 2006], it might be possible that this area is strongly involved in the context of meditation, because of the ongoing scanning of ones own body in some traditions, as is the case for Insight Meditation. And as meditation aims at a reduction of executive attention, the spatial aspect of cognition might become more dominant and maybe the same holds true then for the processing within the left superior frontal gyrus.

As pointed out earlier, meditation, especially the volitional aspects of it, is believed to be associated with an increased activation of the prefrontal cortex, particularly in the right hemisphere, and the cingulate gyrus [Newberg & Iversen, 2003], reflecting the required intense focus of attention. But as the cingulate gyrus seems to be functionally divided into an anterior executive and a posterior evaluative region [Vogt et al., 1992], the current findings have to be interpreted with some extra caution: The anterior cingulate cortex has been reported

earlier as playing an important role in brain activity induced by transcendental meditation [Yamamoto et al., 2006]. The role of the posterior cingulate in the context of meditation though cannot be address so straightforward: Researchers speculated about its role in processes involving emotion and memory and its possible involvement in anxiety disorders [Maddock & Buonocore, 1997, Maddock et al., 2003]. Also it was suggested that the posterior cingulate gyrus contributes to memorizing topographical [Katayama et al., 1999] and autobiographical [Maddock et al., 2001] information. Yet, more important for the purpose of this discussion is a study, which appears to show that the posterior cingulate and the medial prefrontal cortex establish a kind of neural interface between attention and motivation [Small et al., 2003]. This conclusion is underpinned by the finding that in monkeys the medial nucleus of the pulvinar is connected with the posterior limbic neocortex, i.e. the posterior cingulate cortex, thus being part of the neural network responsible for modulating directed attention [Baleydier & Mauguiere, 1985]. Interestingly, there have been connectivity studies indicating a functional relationship between the hippocampus and the posterior cingulate gyrus, too [Heun et al., 2006].

Combining these evidences with cases of posterior cingulate epilepsy, midcingulate lesions, observations from stroke and vegetative state patients, blood flow studies during sleep and facts about general anesthetics researchers concluded that the posterior cingulate plays a key role, together with the precuneal and retrosplenial cortices, in creating consciousness. Especially the ability of self-reflection might be sited in posterior cingulate and precuneal cortices [Vogt & Laureys, 2005]. Thus in sum, the association between gray matter concentration and meditative experience in the left as well as in the right posterior cingulate cortex that was found in this study might very well be the result of the enhanced self-reflective work that is applied during the course of meditative practice. It is worth mentioning that in nearly all analyses conducted in the course of this study the left and right precuneus varyingly appeared to be significant in the according a-priori ROI-analyses. But as there were no expectations or assumptions concerning this brain region at the beginning of this study, these results were not reported. So, this should actually be a region future research should pay especially attention to.

Meditating men showed a gender-specific result, as only they had greater gray

matter density compared to their control subjects in the right inferior temporal gyrus. In humans the superior temporal cortex is known to be responsible for spatial awareness [Karnath et al., 2001], while the inferior temporal cortex is involved in visual perception [Onitsuka et al., 2004]. Other researchers even believe that awareness of object identity might be associated exclusively with activity at or beyond the anterior part of the inferior temporal cortex [Bar & Biederman, 1999]. As already mentioned when discussing the fusiform gyrus meditation involves enhanced alertness to the own body and therefore might even incorporate visual imagery of certain body parts, what might be the reason for the found occupation of brain areas responsible for spatial awareness and visual perception. That this finding occurs only in men is not surprising by all means, because researchers found for example that in visual perception tasks age and sex modified factors in the silhouettes, object decision, progressive silhouettes, position discrimination, and cube analysis subtests of the Visual Object and Space Perception Battery significantly [Herrera-Guzman et al., 2004].

Yet, it is surprising that in this analysis no significant result was found in the hippocampus. Also an additional voxel-based ROI-analysis in only meditating men with their corresponding change in breathing rate as indicator for meditative experience could not find any significant results in either hippocampus. Instead there was even a trend in the hippocampal head to be higher in gray matter concentration in controls than in meditators. This might point to the fact - and researchers have shown this earlier [Pruessner et al., 2001] - that the morphology of the hippocampal formation has to be analyzed in even greater detail with adequate methods. This, e.g. to test, whether meditation might have different effects on hippocampal head and tail, must be put on the agenda of following studies. In this connection it is necessary to bring up the matter of hippocampal volume in general again: For the purpose of this study the assumption was made at the beginning of this section that in contrast to women male hippocampal volume undergoes a decline with advancing age. It is still unknown though, at what point this process might start. Mentioned before was a study that suggested even young adulthood [Pruessner et al., 2001]. And the current study pursued this conclusion at least implicitly. But this is disputable, because researchers could show that elder adolescent subjects had significantly more gray matter in the left medial temporal regions than younger adolescent subjects and significantly less gray

matter in the left medial frontal region. And the volume of the hippocampus was found significantly larger in male elder adolescents than in male younger adolescents [Suzuki et al., 2005]. So, here it is to determine at which stage of life the process of hippocampal degeneration in men exactly starts. But moreover there are still other researchers, who could not find any evidence for the hypothesis that male hippocampal volume decreases over time: In an according VBM-study in 465 normal adults global gray matter volume decreased linearly with age, with a significantly steeper decline in males. Local areas of accelerated loss were observed bilaterally in the insula, superior parietal gyri, central sulci, and cingulate sulci. But areas exhibiting little or no age effect were noted in the amygdala, hippocampi, and entorhinal cortex. There was no interaction of age with sex for regionally specific effects [Good et al., 2001]. Thus, although the assumption was made that hippocampal volume declines in men over time, it should be stressed at this point that this assumption is controversial.

This study revealed that in women a specific region, namely the left thalamus, was higher in gray matter density comparing meditating women with female non-meditators. Again referring to the Newberg-Iversen-Model of the mechanism underlying meditative experience [Newberg et al., 2001] this outcome can be easily explained by the innervation of the reticular nucleus of the thalamus by the prefrontal cortex as part of the global attentional network. The subsequent stimulation of the hippocampus as derived earlier is then in a sense inevitable, if one thinks of the functional connectivity of the thalamus and hippocampus [Stein et al., 2000]. Why this result could only be found in women though, remains open.

As the results of the manual as well as the automated analyses suggest that there are different effects of meditative practice in men and women, it might also be interesting to look into an according combined manual segmenting-VBM-analysis that would test for the effect of meditative experience in men and women separately. As there were only seven female practioners involved in the current study the sample size was to small to conduct such an analysis. So, this remains a task for future research, too.

Finally, a study might shed some light on how complicated the whole complex of topics might potentially be: In an fMRI study that explored the neural correlates of attentional expertise in long-term meditation practitioner researchers found that activation in a network of brain regions typically involved in sustained attention showed an inverted u-shaped curve in which expert meditators with an average of 19,000 hours of practice had more activation than novices, but expert practitioners with an average of 44,000 hours had less activation [Brefczynski-Lewis et al., 2007].

General Methodological Remarks

In general it can be ascertained now that it is useful to combine different automatic methods, or even manual and automated methods respectively, because the current study among others could show that results may be quite divergent: VBM was not able to replicate the difference in male hippocampal volume that was found by the manual segmentation (this holds true independently of certain thresholds: a visual examination of the data showed that VBM could not find any differences in male hippocampal volume whatsoever, not even a trend). Maybe the resolution of VBM is even to low in general to examine structures of the size of the hippocampus reliably. But still VBM was able to detect differences in gray matter density in subcortical structures that a cortical thickness analysis would have been unable to find.

Taking the posthoc power of the according statistical tests into consideration it turns out that given the maximal observed effect size of F(32) = 2.690 there was a less than 10% change of finding a significant result with a sample size of 35 subjects. Maybe this will even turn out to be one of the most serious problems that researchers within the area of meditation research will have to face. Because not only is it rather expensive and complex to conduct brain-imaging studies, but also it is hard to find enough participants with an appropriate and adequate profile of meditative practice. In this context it is interesting to take a look to one of the most sophisticated current attempts to shed light on the effects of meditation on the human brain: In 2006 the Center for Mind and Brain at the University of California, Davis, in cooperation with the Santa Babara Institute of Consciousness Studies started a longitudinal study on the effects of intensive meditation practice on attention, emotional regulation, and their neural correlates. The project studies 30 participants in a one-year residential retreat, where they will practice meditation (Shamatha) 8-10 hours per day. Although the neural correlates might not be the only focus of the project, still it seems suitable to ask the question, whether this kind of intervention is able to induce changes on a

morphological level in the brain at all, and if so, whether the effect might be large enough to be detected. Declaredly it is unclear at this point, what might induce a stronger effect: An intense practice over a rather short time period, or a more moderate practice over a longer period of time. But considering that the present study examined meditators with an average experience of 9.1 ± 7.1 years, who practiced 6.2 ± 4.4 hours per week, it seems at least doubtful that the mentioned study will be able to create stronger effects than the present one. Therefore, researchers in future studies should start to use the effect sizes of comparable previous work to calculate the number of subjects needed for adequate power to detect significant differences between groups.

Like other complex, multifaceted interventions, meditation represents a mixture of specific and non-specific elements of effects. However:

"(...) meditation is somewhat unique in that it is difficult to standardize, quantify, and authenticate for a given sample of research subjects. Thus, it is often challenging to discern its specific effects in order to satisfy the scientific method of causal inferences that underlies evidence-based science." [Caspi & Burleson, 2005]

Among the challenges researchers have to face are the mismatches between questions and designs, the variability in meditation types, problems associated with meditation implementation, and individual differences across meditators [Caspi & Burleson, 2005]. As researchers handle such a complex experience like a meditative state, there is also a large variety of confounding variables, some of which this study unavoidably had to deal with as well, e.g. age, gender, type of meditation, meditation experience, race, years of education, self-selection, genetics, handedness, specific mental exercise, stress hormones and immune functioning. In case of functional imaging studies the impact of the technical environment that might impair relaxation, and might even more change the cardiovascular functioning, is an additional variable to consider. Here, one outcome of the current study should be stressed again explicitly: Researchers should be advised of screening for attentional skills when conducting future research in the field of meditation, because this study in line with a number of other studies mentioned before points to the strong interdependencies between attentional networks and the neural structure that is the basis of meditative experience. For this purpose questionnaires like the Attentional Network Test [Fan et al., 2002] or even behavioral tests could be used.

CONCLUSION

Although related to other mechanisms like the ones underlying attention, at the moment it is still believed that meditative experience is associated with a special neural activity and circuitry [Neumann & Frasch, 2006]. And as this study alone could proof, there are many interesting open questions, with implications to a wide range of related disciplines and fields of research, e.g. attention, degenerative brain diseases or gender differences in brain morphology.

In line with the results of the current study, it seems that there are two

different directions future research should focus on: On the one hand - as already described in the introduction - researchers should try to relate the neurobiological, neurochemical and neuroanatomical findings with psychological dimensions.

Interestingly quite early - in the late 1970'ties - studies began to systematically explore the influence of meditation on the human personality

[Akers et al., 1977, Grace, 1976, Smith, 1978, Williams et al., 1976], but then it seems as if science lost interest in the topic and only in recent years the open questions were addressed again [Takahashi et al., 2005, Wright, 2007]. It is therefore so much more important to get back on the track and integrate especially the results of modern brain

imaging methods into the current understanding of meditation and its underlying

processes and human personality.

On the other hand advanced imaging techniques could be applied to get a better and more detailed understanding about the neuronal circuits that are at the basis of meditative experience and its impacts on human consciousness. Concretely, this could initially include fMRI studies using a stress task to induce moderate psychosocial stress in a scanning environment to test for differences in functional processing between meditators and controls. Further analyses could use manual or automated volumetry and cortical thickness measurements in combination with EEG and Diffusion Tensor Imaging (DTI) [Le Bihan et al., 2001] in conjunction with functional connectivity analyses [Cordes et al., 2000] to determine how effects can come about in terms of mutual interactions between the brain areas, which already have been found to be involved in creating the meditative experience. Especially a DTI study seems very promising, as at the momentary stage enough data from EEG,

PET, MRI, fMRI and other brain imaging studies is available to test the validity of the models of attentional and meditation research in terms of interactions between the described brain areas. Because the most advanced application of DTI is that of white matter fiber tracking and visualization in the brain, which, in combination with fMRI data, might open a window on the important issue of connectivity. This is the only way to determine how activated areas are linked together as networks, i.e. the only way to test models about the underlying mechanisms, particularly the Newberg-Iversen-Model [Newberg & Iversen, 2003]. The combination of the outcome of a combined fMRI-DTI-study with additional data of anatomical studies might then be able to provide researcher with a truly meaningful and sound overall picture.

Conclusively it has to be mentioned that especially longitudinal studies would be of great help to get a deeper understanding of what effects meditational practice really has and how it bears its impact on the practitioner [Rani & Rao, 1996, Valentine & Sweet, 1999]. Maybe this combined with sufficient personality assessment could be a way to get a grip on the problem of self-selection in practioners samples, either by starting off with a really randomly chosen sample, or at least by enabling the researcher to analyze this aspect of his population more fundamentally.

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